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DOI

[10.1111/risa.14318](https://doi.org/10.1111/risa.14318)

Publication date

2024

Document Version

Final published version

Published in

Risk Analysis

Citation (APA)

Hamilton, K. A., Ciol Harrison, J., Mitchell, J., Weir, M., Verhougstraete, M., Haas, C. N., Nejadhashemi, A. P., Libarkin, J., Medema, G., & More Authors (2024). Research gaps and priorities for quantitative microbial risk assessment (QMRA). *Risk Analysis*, 44(11), 2521-2536. <https://doi.org/10.1111/risa.14318>

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Research gaps and priorities for quantitative microbial risk assessment (QMRA)

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Funding information

QMRA-IV, Grant/Award Number: R25GM135058-01

Abstract

The coronavirus disease 2019 pandemic highlighted the need for more rapid and routine application of modeling approaches such as quantitative microbial risk assessment (QMRA) for protecting public health. QMRA is a transdisciplinary science dedicated to understanding, predicting, and mitigating infectious disease risks. To better equip QMRA researchers to inform policy and public health management, an Advances in Research for QMRA workshop was held to synthesize a path forward for QMRA research. We summarize insights from 41 QMRA researchers and experts to clarify the role of QMRA in risk analysis by (1) identifying key research needs, (2) highlighting emerging applications of QMRA; and (3) describing data needs and key scientific efforts to improve the science of QMRA. Key identified research priorities included using molecular tools in QMRA, advancing dose–response methodology, addressing needed exposure assessments, harmonizing environmental monitoring for QMRA, unifying a divide between disease transmission and QMRA models, calibrating and/or validating QMRA models, modeling co-exposures and mixtures, and standardizing practices for incorporating variability and uncertainty throughout the source-to-outcome continuum. Cross-cutting needs identified were to: develop a community of research and practice, integrate QMRA with other scientific approaches, increase QMRA translation and impacts, build communication strategies, and encourage sustainable funding mechanisms. Ultimately, a vision for advancing the science of

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QMRA is outlined for informing national to global health assessments, controls, and policies.

KEYWORDS

coronavirus disease 2019, environmental health, pathogens, quantitative microbial risk assessment, risk analysis, safety

1 | INTRODUCTION

1.1 | A call to advance the field of quantitative microbial risk assessment (QMRA) to tackle urgent problems

The coronavirus disease 2019 (COVID-19) pandemic has demonstrated the dire need to bolster the early identification of infectious disease transmission and act quickly to mitigate risk (Beatrice & Calleja, 2021; Diamond et al., 2022; Pluchino et al., 2021). Building capacity for conducting quantitative microbial risk assessments (QMRAs) and integrating those efforts into policy decision support systems can increase disease prevention and resilience. Further refining the knowledge underlying risk assessment such as the linkages between microbiology, medicine, exposure science, and other fields is needed. Additionally, understanding how QMRA outputs interface with policies, engineering management strategies, and public health levers for intervention will increase the quality and relevance of the field. Although the QMRA community of scientists has grown around the world, there is a lack of coordination to ensure continued growth in productive directions. Continued improvement of QMRA methods and practices is needed to support 21st century water and food safety, and control of emergent and re-emergent infectious diseases.

In support of these goals, our objectives were to bring QMRA scientists together to identify: (1) key research gaps in the field of QMRA; (2) emerging applications of QMRA; and (3) data needs and key scientific efforts for addressing gaps and driving new applications. This perspective aims to synthesize research gaps and top issues to advance QMRA education and user communities in support of those needs to advance the field of QMRA.

2 | QMRA BACKGROUND

2.1 | Defining the field of quantitative microbial risk assessment (QMRA)

Transdisciplinary or convergent research is defined as “research efforts conducted by investigators from different disciplines working jointly to create new conceptual, theoretical, methodological, and translational innovations that integrate and move beyond discipline-specific approaches to address a common problem” (Aboelela et al., 2007). QMRA is a transdisciplinary field dedicated to quantifying risks

posed by exposure to pathogenic microorganisms in various matrices (such as food, water, air, soil, and fomites) and through various exposure routes or scenarios (e.g., aerosol inhalation, contact with surfaces, or ingestion of water and food) to inform management efforts. QMRA applications have primarily focused on human health risks, with emphasis on drinking water quality (Rosen et al., 2017), food safety, recreational water (Ashbolt et al., 2010; Boehm & Soller, 2020), biosolids and manure land application (Burch et al., 2017; Gurian et al., 2012; Jahne et al., 2015), homeland biosecurity (Hong & Gurian, 2015; Mitchell-Blackwood et al., 2011), and water reuse (Amoueyan et al., 2017; Hamilton et al., 2018; Jahne et al., 2017; Salveson & Soller, 2019; Schoen et al., 2014). Additionally, applications have included indoor microenvironments such as evaluating disinfection product design and strategies to reduce fomite and airborne transmission (Adhikari et al., 2019; Chabrele et al., 2018; Reynolds et al., 2022; Ryan et al., 2014), as well as hospital acquired infections (Adhikari et al., 2019).

QMRA has demonstrated utility across multiple sectors, which could be expanded to further concerns, including emerging pathogens like fungi, animal, and plant health (Andrade-Mogrovejo et al., 2022), antimicrobial resistance (Schoen et al., 2020), sensitive subpopulations (Opsteegh et al., 2011; Xiao et al., 2012), setting health-based guidelines (Jahne et al., 2017, 2023), and improving water and sanitation services in low- and middle-income countries (Guzmán Barragán et al., 2022; Verbyla et al., 2019). Expansion of QMRA to other applications would provide multiple benefits, including advancing a systematic approach for evaluating pathogen hazards, providing an evidence base for policy decisions, increasing transparency for informing such decisions, and using scarce resources more efficiently.

2.2 | The QMRA framework

QMRA approaches have been developed from principles historically proposed in environmental health and toxicology and can be tailored to specific goals or risks being assessed. The QMRA process includes phases of assessment and analysis for hazard identification, exposure assessment, dose–response analysis, and risk characterization (Haas et al., 1999, 2014). Figure 1 shows the framework and processes involved in completing a QMRA within the context of a broader risk analysis. The hazard identification step is used to identify the pathogens and transmission routes that are relevant to address particular problem formulations or scenarios

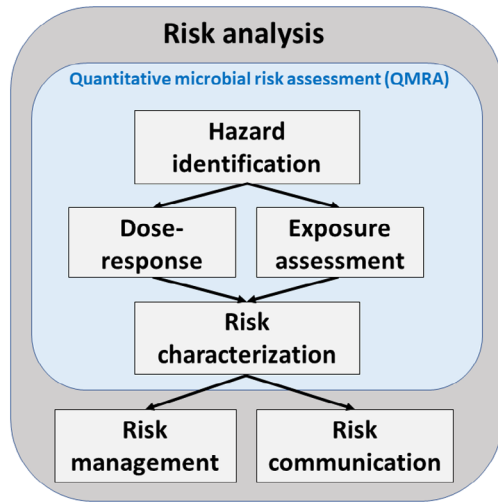


FIGURE 1 Quantitative microbial risk assessment framework within the context of risk analysis.

and modeling goals. During this step, medical and epidemiological data are often reviewed to support the selection of pathogens of concern; however, quantitative data available for many pathogens and settings are limited. In applications where information about the hazard is limited, which can often be the case, especially in resource-limited settings, hazard identification may involve the selection of a reference pathogen(s) to serve as representative organisms for narrowing the assessment scope. Exposure assessment describes pathogen concentrations, occurrence, persistence, human behaviors, and transport from the emission source to the receptor. Dose–response assessment applies an empirically determined mathematical relationship between the amount of pathogen exposure (dose) and the probability of adverse health outcomes (e.g., infection, illness, or mortality). Risk characterization computationally integrates each of the previous components to calculate risk for a given pathogen in a specific exposure scenario among a particular susceptible population. For risk management purposes, calculated risks are often compared to a risk benchmark (target risk) chosen based on the policy context (Sinclair et al., 2015). Specific benchmarks are not typically established for individual countries; however, there are exceptions (Olivieri, et al., 2016; Hultquist, 2016; Natural Resource Management Ministerial Council (NRMCC), Environment Protection and Heritage Council, & Australian Health Ministers’ Conference et al., 2006; Sinclair et al., 2015; World Health Organization, 2006). In some cases, like for drinking water exposures, a 1 in 10,000 annual probability of infection has been suggested (Regli et al., 1991). A 1 in 10,000 benchmark for infection per person per year was adjusted for a daily risk target of 2.7×10^{-7} and used as a basis for California’s pathogen removal requirements for potable reuse (California State Water Resources Control Board, 2022). Additionally, both the World Health Organization and Australian govern-

ment specify 10^{-6} disability adjusted life years (DALYs) for informing policy decisions. Comparative risk assessment can also be performed to evaluate trade-offs between multiple risks (e.g., microbial vs. chemical risks). Risk metrics that are reflective of disease burden (e.g., DALY and quality adjusted life year) can also be used in cost-benefit and other decision analyses (Bergion et al., 2018; Petterson, 2016). Risk analysis is a comprehensive and holistic process that encompasses risk assessment along with risk management and risk communication (Aven, 2016). Despite the focus of QMRA on assessment, we recommend considering risk management and risk communication as part of a broader QMRA process that bridges a quantitative assessment with decision-relevant actions.

2.3 | QMRA as a transdisciplinary field of science

QMRA has evolved as a comprehensive and transdisciplinary science that uses a variety of convergent methodologies, tools, and models from disciplines such as medicine, public health, microbiology and molecular biology, epidemiology, engineering, occupational hygiene, mathematics, and data science, among others (Table 1). QMRA aims to promote an understanding and prioritization of risk drivers to inform management, and in some cases, policy decisions under uncertainty and mitigate infectious diseases transmitted through the environment. Integrating data and approaches from multiple disciplines within QMRA have led to innovations to better identify, quantify, predict, and intervene to reduce risk. For example, QMRA uses statistical and mechanistic models in concert to predict infection and/or adverse health outcomes. Mechanistic models describe the causal relationships using fundamental knowledge of the basic biological, chemical, and physical processes involved; such models are used in both dose–response analysis (to describe the host–pathogen interaction) and exposure assessment (to describe the fate and transport of the pathogen in the environment) (Hamilton, Weir, et al., 2017; Mraz et al., 2020; Mraz & Weir, 2018). Parameters for these models are often estimated from empirical information (e.g., experimental inactivation rates for a pathogen as a function of temperature and environmental matrix) (Hamilton, Ahmed, et al., 2017; Heida et al., 2022) as well as expert opinion and estimated ranges (Morgan et al., 1990). Increasingly, capturing pathogen transmission from host-to-host or from host-to-environment-to-host has become an important mechanism to incorporate into QMRA applications. Disease transmission models (e.g., susceptible-immune-recovered models) provide a dynamic feature that captures how risk can evolve over time as an outbreak progresses (Brouwer et al., 2017; Collineau et al., 2020; Li et al., 2009; Weir, 2020; Weir et al., 2017). Similarly, the use and integration of epidemiological data have furthered QMRA models (Burch, 2020; Enger et al., 2012; Evers & Bouwknecht, 2016; Siettos & Russo, 2013; Soller et al., 2016).

TABLE 1 Quantitative microbial risk assessment (QMRA) as an integrated discipline: example modeling frameworks where QMRA has been integrated or performed in parallel.

Discipline	Modeling approaches commonly used	Applications	Example types of research questions	Strengths (+) and limitations (–)	References
Environmental engineering and environmental microbiology	Quantitative microbial risk assessment (QMRA)	Mechanistic modeling of disease transmission from pathogen source to receptor including ex vivo and in vivo pathogen fate and transport	<ul style="list-style-type: none"> • What is the risk at low dose? • How “clean” is clean enough? • What is the most efficient intervention to limit the spread of infection based on a target risk level? 	<ul style="list-style-type: none"> + Provides increased understanding of risk drivers through sensitivity analysis + Allows for evaluation of mechanistic factors and influence on exposure – Difficult to validate due to low dose extrapolation – Can overestimate risks – Models can require a large amount of information to parameterize – Reliance on literature assumptions – Risks can be underestimated, e.g., by failing to include all pathogens and/or exposure sources 	Haas et al. (1999, 2014)
Clinical medicine, infection control, and public health	Infectious disease transmission models (e.g. statistical models, mathematical/mechanistic state-space models including SIR/SEIR, empirical/machine learning-based models)	Modeling approach to predict infectious disease progression to show the outcome of an outbreak/epidemic and inform public health interventions	<ul style="list-style-type: none"> • What is the reproduction number of a particular infectious disease? • What is the predicted progression of epidemics and/or outbreaks? • What interventions will most effectively reduce transmission? 	<ul style="list-style-type: none"> + Takes into account person-to-person transmission + Can be combined with phylogenetic models – Models can be complex and require many inputs; inconsistency among datasets can be problematic 	De Angelis et al. (2015), Siettos and Russo (2013), Tang et al. (2020)
	Epidemiological studies	Study and analysis of distribution, patterns and determinants of health and disease in defined populations used to determine trends at the population level using multiple study designs (e.g. case-control, cohort, case cohort, ecological)	<ul style="list-style-type: none"> • What is the reproduction number of a particular infectious disease? • What is the relative risk or odds ratio in an exposed population compared to a control? • What are the spatiotemporal patterns of infection? 	<ul style="list-style-type: none"> + Provides assessment of strength of evidence supporting link between exposure and outcome – Requires large study sizes to detect small effect size; can be time-consuming, costly, and logistically challenging 	Gambhir et al. (2015)

TABLE 2 Results of survey: “What are your top three issues that need to be addressed to advance research for quantitative microbial risk assessment (QMRA) in general or for the components of QMRA (e.g., hazard identification, dose response, exposure, characterization)?” “*n*” = number of respondents who indicated the theme was a priority out of 35 total survey respondents, with overlap in response categories.

Theme identified from survey responses	<i>n</i>	Summary of issues identified by participants that need to be addressed to advance QMRA
Hazard identification	2	<ul style="list-style-type: none"> – New and emerging pathogens
Dose–response	22	<ul style="list-style-type: none"> – Dose–response methods to address uncertainty that account for diversity, preexisting conditions, demographics, adapting dose–response models to other pathogens, and other risk factors (e.g., social factors) – Increasing understanding of host-microbe interactions and diversity of microbial pathogens – Understanding strain differences – More dose–response models, including for additional exposure routes – Dose harmonization between environmental measurements and dose–response units – Methods addressing animal-to-human extrapolation of dose–response functions – Development of cumulative dose models – Improved understanding of virulence factors
Exposure assessment	21	<ul style="list-style-type: none"> – Better understanding of exposure and transmission pathways – Exposure factors for specific under-explored settings – Proportion of viable/infectious organisms, – More data on pathogen presence and persistence in different matrices; persistence differences for different pathogen quantification methods – Improving sensitivity of exposure and pathogen measurement methods, especially for aerosolized pathogens
Risk characterization	5	<ul style="list-style-type: none"> – Models that interface with policy – Separating variability and uncertainty; shifting focus from advanced mathematics on limited data to understanding the outcome and collecting better data
Communication	6	<ul style="list-style-type: none"> – Increased QMRA awareness/“democratizing QMRA” to make it accessible beyond experts – Improving communication of results to the public – Communicating value of QMRA for policy applications
Management	2	<ul style="list-style-type: none"> – Comprehensive evaluation of acceptable risk benchmarks – Connecting QMRA with actionable outcomes
Integration of QMRA with other approaches	12	<ul style="list-style-type: none"> – Integration with epidemiology and transmission models – Integration of machine-learning methods – Tackling antimicrobial resistance
Calibration, validation, and “reality checking” of QMRA models; reproducibility of QMRA models	10	<ul style="list-style-type: none"> – Corroborating QMRA predicted risks with observations – Establishing QMRA publication standards and reporting guidelines – Open access to existing datasets and model codes – Increasing availability of accessible and simple models and frameworks – Clarifying impact of uncertainty and variability on risk estimates
Funding concerns	2	<ul style="list-style-type: none"> – Collaborative approach among QMRA researchers – Funding capacity within agencies; clarification of mission areas for which QMRA is relevant – Training graduate students

3 | WORKSHOP AND SURVEY OVERVIEW

A workshop “Advances in Research for QMRA” was held with 41 total participants. Participants were sent a pre-workshop survey. Prior to the workshop, a recorded presentation was provided summarizing “Envisioning the future of QMRA” (The [Supporting Information](#) section). This highlighted key research and scientific questions to advance the field that the attendees ranked. The workshop was divided into two sessions: “Envisioning the Future of QMRA” and “Next Steps in QMRA Research.” A systematic approach was taken to code responses and workshop themes from two rounds of breakout groups (Section [S1](#)).

4 | SURVEY RESULTS

4.1 | Research themes identified by workshop participants

Thematic survey coding results are shown in [Table 2](#), along with a summary of participant free-form responses. The majority of respondents indicated that dose–response (64.7%) and exposure assessment (61.8%) were of high importance for QMRA research. Common responses indicated that more dose–response models were needed, and that there was an overall need in QMRA for better integration of data using modern molecular tools (e.g., molecular methods for quantifying microorganisms, gene sequencing) (Collineau et al., [2019](#); Karanth et al., [2022](#); Karanth &

TABLE 3 Applications of quantitative microbial risk assessment (QMRA) that participants identified as being useful in the future ($n = 30$).

Primary theme identified from participant comments	No.	Summary of subtopics identified by participants for potential applications of QMRA used to create primary theme area
Integration of QMRA with other fields	8	Behavioral economics, epidemiology, life cycle assessment, artificial intelligence/machine learning
Specific domain areas	24	<ul style="list-style-type: none"> o Recreational water (3): skin infections, risk-based thresholds for microbial source tracking (MST) markers in recreational water, exposures to beach sand, sediments, and aerosols o One Health, including antimicrobial resistance (AMR) (4) delineation of transmission pathways, characterizing importance for water industry o Water reuse (7): best practices for evaluating treatment changes; opportunistic pathogens (4) including aerosol risks and more explicit regulatory treatment or concentration benchmarks o Built environment (4): more involvement in design of buildings/ spaces, infection control o Others (6): fungi, global health, food safety, and public health, biosafety, return to work, climate change, respiratory viruses
Policy/ decision-making	6	More frequent informing of public health policies and decisions, policy analysis for future pandemic response
Application of molecular techniques in QMRA	3	Increased application of molecular and metagenomics techniques and data in QMRA, linking QMRA with MST markers
Monitoring/ choosing indicators/ identifying data collection needs	3	Developing risk-based thresholds for MST markers; using QMRA to determine which pathogens to incorporate into routine monitoring, which surrogates accurately reflect risk, which environmental indicators are the most important predictors of human health, and what new data are needed to decrease uncertainty

Note: "No." = number of respondents who indicated the theme was a priority, with overlap in response categories; numbers in parentheses represent respondents who indicated the subtheme was a priority.

Pradhan, 2023; Tanui et al., 2022). Integration of QMRA with other approaches (35.3%) was indicated, especially with epidemiological methods. Finally, suggestions were made to improve QMRA reproducibility as well as to "reality-check" models or their components (e.g., exposure or dose-response models) by increasing efforts to corroborate QMRA models with infection and/or disease observations (e.g., through retrospective analysis of outbreaks and/or epidemics (Gupta & Haas, 2004; Prasad et al., 2017; Teunis et al., 2008)) and to establish criteria for model reporting.

4.2 | QMRA applications identified by workshop participants

Numerous applications of QMRA were identified and are summarized in Table 3. Most respondents (77.4%) recommended specific domain areas for future study, including recreational water, One Health (including antimicrobial resistance), water reuse, the built environment including infection control, and other categories (fungi, global health, food safety, biosafety, return to work and/or baseline operations after pandemic-related restrictions, climate change, water reuse, and respiratory viruses including aerosol transmission). Integration of QMRA with other fields, such as behavioral economics, epidemiology, life cycle assessment, and artificial intelligence or machine learning analysis, was also suggested (25.8%). Other research areas of interest included again the application of molecular techniques/data in general for QMRA (9.7%), monitoring or choosing indicators to use for QMRA and identifying the path to better collection of data (9.7%). These survey findings were corroborated by the participant live poll ranking of research gaps presented in the prerecorded session (Box 1).

BOX 1. Research gaps presented during the workshop and ranked by participants ($n = 28$ responses, 1 = highest priority)

1. How do we make use of molecular data (on exposure) to assess risk?
2. Coupling of QMRA to disease transmission models for contagious agents
3. New/emerging applications: antimicrobial resistant pathogens and genes
4. Communicating with those who really could benefit from the approach
5. How to describe exposures to pathogens with other stressors (either other pathogens or chemical or physical stressors)
6. More mechanistic models for dynamics of pathogens within hosts
7. How to describe repeated exposures?
8. Best practices for doing QMRA on Agent "X"
9. Emission rates of pathogens: is there a unified framework that can be developed?
10. New/emerging applications: animal pathogens
11. What about fungi?

4.3 | Modeling tools and educational needs

Participants reported up to 25 years of experience with QMRA methods and most ($n = 23$, 65.7%) engaged in teaching activities related to QMRA. Several modeling tools were commonly used in QMRA research, including

BOX 2. Action needed to address major gaps and to advance quantitative microbial risk assessment (QMRA) (gaps identified from survey responses to education-related question)

1. Improve awareness of QMRA as a field by policymakers, employers, etc.
2. Identify sustainable funding sources
3. Establish a community of practice and improving accessibility
4. Fill key quantitative gaps for students
5. Improve education on modeling practices and decision-making
6. Engage students addressing QMRA and modeling earlier in educational process
7. Teach and make the case for QMRA as a complementary, transdisciplinary tool
8. Improve risk interpretation, management, communication of findings and associated uncertainty, and translation
9. Standardize QMRA practices

MATLAB, R, Analytica, Python, Stata, government software, and Excel-based tools (Table S2). These tools can be used for multiple aspects of QMRA models and in most cases interchangeably for stochastic modeling purposes. However, many computational tools have been developed specifically for predictive microbiology and/or QMRA such as open-source R packages (Delignette-Muller & Dutang, 2015; Pouillot & Delignette-Muller, 2010) or other tools (Bundesinstitut für Risikobewertung, 2023) or web applications (Crank et al., 2019; Rocha-Melogno et al., 2021). Common classes of models and approaches spanned multiple disciplines (Table S3). The majority of participants (91.4%) supported the availability of public model codes for QMRA. A brief summary of educational topics raised is summarized in Box 2.

5 | ENVISIONING THE FUTURE OF QMRA

5.1 | Breakout summaries Part 1: What are we missing? What QMRA research/science gaps were not addressed by the presenters?

Research gaps were identified related to the components of the QMRA framework as well as QMRA practices, the use of QMRA in decision-making, and communication of QMRA science with stakeholders (Table 4). Discussion points included which factors inform the selection of reference pathogens and the need for criteria to identify and prioritize such reference pathogens. QMRA models are often developed for water and air exposures but could be

more routinely used to consider other routes (e.g., vector transmission (Capone et al., 2023)). In exposure assessment, additional information from behavioral science studies should be included when developing exposure parameters for QMRA.

The dose–response assessment step of QMRA was a strong area of focus. Key gaps were identified including the need to identify factors affecting variability in host status and its relationship to disease outcomes (including social vulnerability and development, immunity or vaccinations, interactions between other pathogen and chemical exposures as well as the microbiome impacts on risks) (Tables 4 and 5). Consideration of strain and virulence factor differences, approaches to addressing aggregation effects and the resulting impacts on risk estimates (Van Abel et al., 2017), harmonization between environmental measurements and dose–response units (McBride et al., 2013), low-dose extrapolation methods and mechanistic dose–response assumptions (Schmidt, 2015; Teunis & Havelaar, 2000), and cumulative dose model development were suggested areas for additional study. Advanced computational tools such as bioinformatics with high-throughput sequencing data can be used to address some of these linkages if sufficient data are available; however, standardized methods for incorporating these approaches into QMRA models are lacking. Additionally, there is a need for standardized guidance on best practices for acquiring and analyzing dose–response datasets. In the case of the COVID-19 pandemic, for example, early QMRA models (Zhang et al., 2020) relied on coronavirus surrogate models (Watanabe et al., 2010) that were later calibrated using outbreak data and environmental measurements (Parhizkar et al., 2022; Schijven et al., 2023). More explicit dose–response development and proxy selection guidance could inform improved rapid risk assessments during the early stages of novel disease recognition. Some groups of microorganisms generally have few dose–response models available and would benefit from the development of additional traditional dose–response models in addition to the discussed advancements in methods (e.g., helminths or fungi).

Other identified needs included best practices and a common QMRA vocabulary across multiple parts of the QMRA framework. QMRA models inherently involve combining data from different sources (e.g., published literature), and guidance is needed for combining and selecting data for different purposes. Multiple approaches to QMRA are possible (e.g., developing purely mechanistic models vs. combining a QMRA framework with more data-driven approaches such as machine learning). There is a need for understanding how sparse data, as well as different treatments of variability and uncertainty, impact predictions and interpretations in different contexts. Evaluating model parsimony and corroboration of model predictions with observed epidemiological trends is needed, especially as QMRA models become more complex. Increasing transparency of QMRA methodology can aid in translating the findings of QMRA models, and a discussion of what “model validation” means in practice across different parts of QMRA models was recommended for

TABLE 4 Breakout group summaries for “moving quantitative microbial risk assessment (QMRA) forward: Identifying key studies to advance QMRA.”

Topic	Key studies suggested
Hazard identification	<ul style="list-style-type: none"> – Using stakeholder/ community input to define QMRA scope
Exposure assessment	<ul style="list-style-type: none"> – Framework to look at methods for exposure assessment – Uncertainties associated with sampling approach and influence on risk estimates – Producing more human behavior data and integrating social science
Dose–response	<ul style="list-style-type: none"> – Advancing dose–response modeling approaches; methods for extrapolating to emerging pathogens – More animal and human dose–response models – More high-throughput dose–response approaches (e.g., cell culture) – Leveraging existing vaccine trials to coproduce data that are also useful for dose–response – Dose–response approaches for children – Comparing QMRA dose–response with approaches from other fields
Reproducibility in the field of QMRA	<ul style="list-style-type: none"> – Developing a common language for QMRA – Standardizing approaches for study design – Curating datasets for QMRA
Integration with other disciplines	<ul style="list-style-type: none"> – Expanding from origin in engineering to including other disciplines (e.g., social sciences) with large, collaborative, and multidisciplinary approaches – Comparative studies between epidemiology and QMRA
Integrating data generated with molecular methods	<ul style="list-style-type: none"> – Exploring ways to use bioinformatics and genomics to answer questions on virulence, disease outcomes, etc.; how to incorporate molecular data into QMRA as focus shifts from culture-based to molecular-based assays – Systematic review of current literature on infectivity and molecular tools; understanding gene copy to infection unit ratios as a function of environmental factors
Validation/calibration of QMRA	<ul style="list-style-type: none"> – Linking with epidemiology and chemical risk assessment groups to develop criteria for QMRA model validation, reality-checking, calibration, etc. – Comparative studies of QMRA and epidemiological estimates of risk
Decision-making and policy; translating QMRA research into practice	<ul style="list-style-type: none"> – Determining what people think is an “acceptable” level of microbial risk (i.e., benchmarks) – Approaches for combining QMRA with policy decision-making – Approaches for setting QMRA-based concentration targets for environmental monitoring or other standards – Increasing awareness of QMRA science among other fields – Building streamlined models for public communication

additional focus (e.g., comparing QMRA model predictions and observed epidemiological trends and/or outbreaks).

Ultimately, the goal of QMRA is to inform decision-making and communication for health-related goals. To this end, risk benchmarks (e.g., 1 in 10,000 infections or 1 in 1,000,000 DALY per person per year) have been proposed, but such benchmarks raise the need for a broader discussion related to the implementation details, as well as the appropriateness and application of benchmarks across different domains. Microbial risks need to be evaluated within the context of other risks and economic impacts. Best practices for the translation of QMRA applications from model results to decision context, as well as for communication of the results to different stakeholders, would be beneficial for public health. Broader engagement of the QMRA community with other research communities (e.g., risk communication and epidemiology) can help to address these needs.

5.2 | Breakout summaries Part 2: How do we move QMRA forward? Identify two to three key studies needed now to advance QMRA and discuss how these studies would advance the field

Key research studies were proposed related to the identified research gaps (Part 1 above). Several aspects of the

QMRA paradigm, reproducibility in the field, integration with other disciplines to advance specific aspects of the social dimensions of QMRA and use of data generated using molecular methods (e.g., qPCR and high-throughput sequencing results), as well as decision-making and policy related to translating QMRA research into practice were identified (Table 5). Integration with other disciplines, such as social science (e.g., integrating information on compliance with household water interventions (Hayashi et al., 2019)) and epidemiological models of disease prediction (Brouwer et al., 2017), was a common theme in the session. Key studies identified for exposure assessment focused on understanding how uncertainties associated with sampling approaches influence risk. The dose–response assessment was a major focus, with a need for more advanced, high-throughput approaches to dose–response that will be more responsive to emerging pathogens as well as greater numbers and combinations of pathogens. For example, cell culture studies and vaccine trials could be leveraged to produce data useful for dose–response modeling. Comparing estimates from QMRA models using a dose–response with epidemiological data can also help to support efforts to calibrate, validate, or otherwise “reality-check” QMRA models.

Studies designed to translate QMRA research into practice were also identified as a key gap. In particular, the use of methods (e.g., from the social and economic sciences)

TABLE 5 Breakout group summaries for “envisioning the future of quantitative microbial risk assessment (QMRA).”

Topic	Summary of participant comments on envisioning the future of QMRA
Hazard identification and scoping of QMRA models	<ul style="list-style-type: none"> – Development of criteria for identifying reference pathogens and exposure routes; including pathogens that could become more problematic in the future
Exposure assessment	<ul style="list-style-type: none"> – Need to integrate ethnographic studies focusing on human behavior into QMRA – Need for better integration of social vulnerability to understand exposure and risk – Implications of non-detects for treatment targets – Interpretation of molecular data for persistence and risk – Standardization of pathogen viability assessment methods – Need for larger datasets of pathogen persistence and viability for evaluating statistical relationships
Modifying and understanding dose–response	<ul style="list-style-type: none"> – Factors affecting variability in host status, including: social vulnerability and development, immunity, need for new indicators to assess these factors – Interactions between chemicals and microbial risks (e.g., antimicrobial resistance), including using better methods to evaluate these complex interactions (e.g., bioinformatics, high-throughput sequencing) – Understanding dose–response mechanisms (e.g., pathogen virulence and host immunity) to modify existing dose–response relationships for emerging needs – Adjusting for factors such as vaccination dynamics, immunity and repeat infections, and strain variability in dose–response – Expanding beyond dose–response to a more holistic approach – Need for animal models and dose–response relationships (e.g., for helminths) – Need for accessible guidance on how to acquire and analyze dose–response datasets
QMRA modeling practices	<ul style="list-style-type: none"> – Need for modernization of methods used, improved handling of uncertainty versus variability – Data science versus risk/ mechanistic approach – Methods for evaluating model parsimony and value of information – Need for many assumptions for QMRA and lack of data; best practices needed for combining literature data and systematic approach for understanding risk in context where data are scarce – Need for more resources and handbooks for QMRA, for example, summarizing distribution parameters and recent literature – Need for improved transparency; need for a discussion of what validation means for QMRA (e.g., comparison with epidemiological outcomes, exposure model validation) – Need for integration with other fields (e.g., epidemiology)
Use of QMRA in decision-making	<ul style="list-style-type: none"> – Developing and evaluating realistic risk benchmarks (e.g., DALY numbers) and informing discussions with regulators – Evaluating risk trade-offs and including economic aspects – Using QMRA and machine learning to inform decisions – Translating models better for decision-makers – Creating web-based tools to better interrogate QMRA models and reach a broader audience
Communication between QMRA scientists and stakeholders	<ul style="list-style-type: none"> – Developing best practices for communication about QMRA models and their associated variability, uncertainty, assumptions, and limitations with the public – Need for more studies to improve QMRA communication methods – Engaging with additional fields and practitioners who are skilled in communication – Engagement with stakeholders throughout the process to limit controversy and distrust – Making QMRA guidance geared towards implementable strategies
Other	<ul style="list-style-type: none"> – Funding needed to sustain QMRA research – Need for QMRA in other domains such as healthy buildings, opportunistic pathogens, and children’s health risks

to evaluate what risks are considered “acceptable” in order to inform the development of microbial risk benchmarks for different scenarios and populations should be developed. Engaging stakeholders in the early stages of QMRA scoping can encourage the adoption of QMRA results to inform practical decision-making needs. Developing models (e.g., web applications) designed specifically for communicating model results to different audiences can also aid in translating QMRA findings for application in risk policy and management. Funding large, transdisciplinary, and collaborative studies and educational initiatives is needed to support such efforts.

5.3 | Breakout summaries Part 3: What are the top potential funding opportunities for the QMRA community to pursue? What novel funding opportunities can we identify?

Several funding avenues for the QMRA field were identified where the goals of QMRA would address needs within the organizational mission(s) including US federal agencies (e.g., US Department of Agriculture [USDA], US Environmental Protection Agency [USEPA], National Science Foundation [NSF], and Centers for Disease Control and Prevention [CDC]), private industry (e.g., insurance com-

panies, cleaning/disinfection companies, industries involved with safety, and architecture/construction of the built environment), healthcare (e.g., those targeted at healthcare workers), utilities (e.g., collaborating with utilities as funding partners, understanding problems that would benefit from QMRA research, and cultivating research leaders in the water/wastewater sectors), foundations (e.g., the Water Research Foundation [WRF]), and international partnerships.

Opportunities that leverage interdisciplinary collaborations among multiple agencies, such as the National Institutes of Health (NIH)-NSF Ecology and Evolution of Infectious Diseases Initiative program, are exemplary of situations where QMRA could be integrated and better leveraged. Funding opportunities could stimulate multidisciplinary teams, for example, through convergence research. Engaging QMRA professionals at the beginning stages of research planning in this process is critical so that appropriate data are generated to provide the most informative modeling outputs. There is also a need to advance the science of QMRA itself during research studies. Throughout the COVID-19 pandemic, wastewater-based epidemiology (WBE) has become standard practice. Consequently, opportunities to expand pandemic-related funding opportunities, data dashboards, and research should be seized to integrate with and advance QMRA. Coupling WBE data for assessing both community health and potential wastewater-associated risks (e.g., fecal-oral pathogens or antimicrobial resistant microorganisms) would improve the understanding of risk changes over time, pandemic response, and pandemic preparedness while contributing to epidemiology and risk assessment linkages (Naughton et al., 2023a, 2023b; S. McClary-Gutierrez et al., 2021; Wigginton et al., 2021).

Several other specific research concepts for funding were identified, including focusing on biostatistics method development for combining approaches with QMRA methods and examining microbial risks in terms of interactions. Additionally, opportunities targeting understudied and/or recalcitrant pathogens to understand their inactivation/removal, persistence, and dose–response would be beneficial (e.g., *Toxoplasma* spp. and fungi). There is a need for the creation of frameworks and a common language to make QMRA data/databases and models more interoperable, so that they could be used to answer infectious disease questions at a larger scale.

5.4 | Need for sustained support for QMRA research

QMRA predictions have been shown to accurately estimate illness rates when compared to epidemiological studies, for example, a QMRA for beachgoers encountering microbial contamination (Soller et al., 2017) matched predictions from data collected from a more costly and logistically intensive epidemiologic study (Arnold et al., 2017). QMRA, combined with cost estimates such as cost–benefit or cost-effectiveness assessments, can help to guide efficient resource investment

for pathogen risk reduction (Arden et al., 2020; Drechsel & Seidu, 2011; Machdar et al., 2013). QMRA, therefore, represents a potentially cost-effective method for prioritizing health-risk interventions, although quantitative cost–benefit assessments of QMRA itself compared to other microbial disease assessment approaches have not been performed.

Given the potential for QMRA to conserve and prioritize public health resources, considerations for sustainability of the field of QMRA are warranted. Several issues related to sustaining funding sources for QMRA were raised during the workshop. Multi-field approaches are needed but can be more challenging to fund due to the collaborative, applied nature of risk assessment work falling into a gap between what agencies will fund in different fields. The QMRA field needs outreach to educate funding stakeholders on the value of QMRA approaches for addressing complex problems in infectious diseases. Obtaining buy-in from regulatory agencies can enhance QMRA and create opportunities for integration with regulatory decision needs. Developing best practices and common terminology and continuing to build the QMRA community can help increase the credibility of the QMRA field and aid in efforts to enhance partnerships for QMRA research. More sustainable sources of funding are needed to encourage research as well as educational training opportunities (e.g., student fellowships).

To put QMRA research funding in context, from 2000 to 2017, an estimated 105 billion USD was spent by G20 countries on infectious disease research (Head et al., 2020). In the United States alone, projected 2022 infectious disease research expenditures were approximately 8 billion USD. A preliminary landscape analysis of funding mechanisms for QMRA was completed by examining publicly available data from the United States through a search of public databases for USEPA, the NSF, the USDA, the NIH, and the WRF. Additionally, the Scopus database was searched in the search fields (“Funding information” OR “Funding sponsor” OR “funding acronym”) for the keywords (“QMRA” or “quantitative microbial risk assessment”). Seventy-nine records were returned and five were deemed irrelevant to QMRA. The acknowledgements and funders of each record were reviewed and included in Table S4 when specific grant numbers were referenced, with a focus on US-based institutions. Additional grants are tabulated in the Supporting Information section.

The results indicated that QMRA funding to date has been piecemeal. Although additional federal agencies such as the CDC and Department of Defense, along with other foundations, support QMRA related efforts, public databases of their funding were not available so their contributions could not be included. It was estimated that a total of 56.9 million USD had supported research that includes some component of QMRA science from 2001 to 2020 via four main agencies and two nonprofits, USEPA (32.4 M USD), NSF (13.5 M USD), NIH (6.1 M USD), USDA (2.6 M USD), WRF (2.2 M), and the Obama Singh 21st century knowledge initiative (<0.2 M). These studies focused on a variety of topics related to water, agriculture, food safety, and public health (Table S3). Therefore, 20 years of QMRA research in the US have comprised

less than 1% of the current annual US expenditures on infectious disease research, without correcting for the change in value over time. We argue that an expansion in the QMRA-related research portfolio would provide critical insights into public health interventions using a cost-effective approach.

5.5 | Next steps in QMRA research

One of the key discussion points at the workshop was how to integrate QMRA with other fields of science and professions. Research that is broad and transdisciplinary, for example, addressing the basic science of host-microbe dynamics and microbial pathogenesis using computational biology, would bring insights into the probability of health outcomes in various exposed populations. To expand and improve exposure science, funding with the explicit inclusion of interdisciplinary approaches should be part of the QMRA research portfolio. For example, knowledge of behavior science can be used to define distributions for behavioral compliance variables for assessing pathogen reduction within a QMRA model (Hayashi et al., 2019), and agent-based approaches can be used to understand pathogen persistence given variability in human activity patterns (Mokhtari & Doren, 2019). Additionally, greater integration of molecular biology methods can enhance assessments of pathogen occurrence, fate, and transport and allow for proper consideration of methodological limitations within uncertainty propagation approaches. Integration with medical fields, epidemiology, and public health can inform assessments of disease circulation and person-to-person transmission, host susceptibility, and microbial pathogenesis within QMRA models.

The COVID-19 pandemic has highlighted the challenges associated with risk communication when addressing disease spread, outbreaks (pandemics), and event-driven risks for public health and medical practitioners. Improving the science of communicating probabilities of pathogen risks of exposure and outcomes is critical to promoting management strategies (without producing unnecessary anxiety), building trust, and implementing improved policies. This includes being able to address the cost-benefits and economics associated with pathogen risks under various scenarios.

The interdisciplinary nature of QMRA enables it to interface with and advance the understanding of risk for other professional applications. The use of QMRA has evolved within the water and food industries, particularly for addressing the safety of drinking water, water reuse schemes, and food safety. Some of the major needs, however, are now focused on some of the more complex, recalcitrant, and emerging hazards (i.e., antibiotic resistance, helminths, and opportunistic pathogens), as well as exploring simplified QMRA methodologies in data scarce regions of the world for international development. Additionally, using the QMRA framework for exploring hazards, exposures, and dose-response would benefit the understanding of risk characterization for animal health and the One Health arena. The incorporation of QMRA science would improve understanding of climate change

impacts and climate disaster-driven assessments as well as enhance environmental justice (EJ) evaluations. Enriching EJ decision-making is critical, given the potential for greater exposure to disease-causing microorganisms in some environments.

The use of QMRA within the built environment, including fomite and air exposures beyond medical institutions, can be expanded to include, for example, schools and entertainment establishments (e.g., cruise ships), providing innovative insights into specific populations and exposure scenarios. The QMRA framework provides an ideal approach for informing public policies to prevent disease spread in institutional settings. The QMRA approach can be leveraged alongside pandemic preparedness approaches for the next major “Pathogen X” or “Agent X” to enable faster and improved responses to pathogen crises (World Health Organization, 2023, 2024).

Finally, the QMRA research enterprise needs to be interlinked with education. This could be done by promoting courses, certificates, and programs in QMRA such as the educational activities listed in the last column of Table 2, including the ongoing QMRA IV project. The next generation of scientists with knowledge of QMRA will benefit engineering, medicine, veterinary medicine, the food and water industries, and local to global health professions, thus ultimately improving assessment, management, and policies to address disease-causing microorganisms.

6 | CONCLUSIONS

QMRA can play a critical role in integrating science and shaping policy for managing infectious diseases, pandemics, and emerging pathogens in an ever-changing world. Awareness of the utility of QMRA is increasing among end-users (e.g., government agencies and infection control managers). A virtual workshop, surveys, and literature synthesis were conducted aimed to identify key research gaps and emerging applications of QMRA as well as to identify scientific needs. Significant data gaps and research priorities included recommending a focus on foundational science to advance QMRA and its integration with other fields (e.g., molecular microbiology, immunology, toxicology/ dose-response, computational biology, epidemiology, social sciences, and others). Research needs and data gaps identified to advance QMRA will require the integration of modern, higher throughput tools and approaches for “-omics” and dose-response testing, sensitive exposure monitoring, and advanced computational tools to predict and validate risk for humans, plants, and wildlife (Figure 2).

QMRA makes use of a diverse range of primary and literature-based data sources to populate probabilistic models. As such, considerable expertise is required to evaluate data quality and integrate information from multiple sources to form a comprehensive assessment on a generalized or site-specific basis. In support of the data needs identified, libraries or repositories and databases are necessary to support the

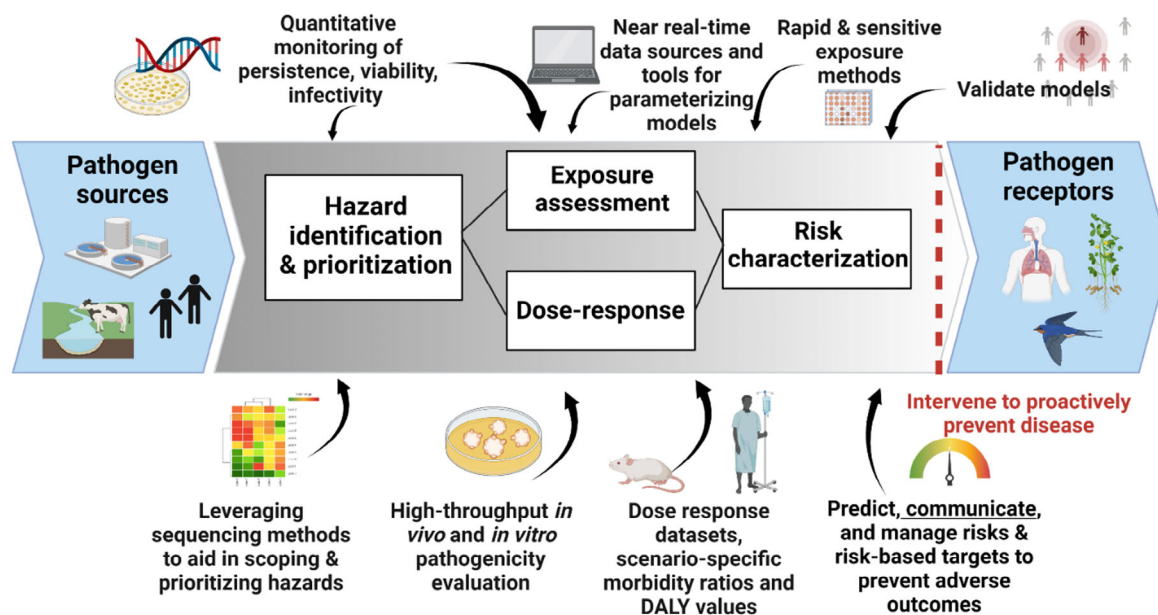


FIGURE 2 Vision for a path forward in quantitative microbial risk assessment (QMRA) to leverage advanced technologies to intervene and prevent disease.

gathering of information and access to new advances. These sources include:

- Updating the QMRA wiki (a repository for data and models currently hosted at <http://qmrwiki.org>) with key findings from new research;
- Providing a centralized code repository and interaction interface (which may or not be the Wiki), perhaps using version control systems like GitHub;
- Creating a central literature database for QMRA article citations and research;
- Increasing communication among QMRA researchers, end-users, and policymakers.

QMRA is a true convergent activity that requires the synthesis of knowledge from engineering, public health, biological sciences, and social sciences. As such, progress in QMRA does not fall neatly into the portfolio of any single funding agency. Hence, advancing this convergence will require deliberate collaboration between multiple agencies (including USDA, NSF, NIH, USEPA, DOD, and others). This synthesis suggests the potential for an interdisciplinary/interagency program to fund quantitative research that supports investigating the probabilities of infection and disease via QMRA, as well as the impact of interventions for mitigation and control by nonmedical means. Interdisciplinary funding opportunities would promote the building of datasets for new hazards, exposure scenarios, and disease control strategies.

Finally, educational efforts are needed to expand the number of trained QMRA practitioners to build a competent government, industry, and public health workforce in the future. Likewise, a dedicated community of practice is needed to support the ongoing development and coordina-

tion of the field. Overall, this will translate QMRA research into complementary toolsets that will improve the long-term understanding of disease risks for local, national, and global health protection goals.

ACKNOWLEDGMENTS

This workshop was organized by Kerry A. Hamilton and Joan B. Rose in collaboration with Jade Mitchell and Mark Weir with NIH funding through QMRA-IV (R25GM135058-01). The authors gratefully acknowledge students who assisted with the workshop data collection, including Gwyneth Dunbar, Rebecca Ives, Andri Rachmadi, Sam Carbonell, Emma Rutin, and Kaitlyn Hutchins. The views expressed in this article are those of the authors and do not necessarily represent the views or the policies of the U.S. Environmental Protection Agency, the US Food and Drug Administration, or the US Department of Agriculture. Any mention of trade names, manufacturers or products does not imply an endorsement by the United States Government or the U.S. Environmental Protection Agency.

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SUPPORTING INFORMATION

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How to cite this article: Hamilton, K. A., Ciol Harrison, J., Mitchell, J., Weir, M., Verhougstraete, M., Haas, C. N., Nejadhashemi, A. P., Libarkin, J., Gim Aw, T., Bibby, K., Bivins, A., Brown, J., Dean, K., Dunbar, G., Eisenberg, J., Emelko, M., Gerrity, D., Gurian, P. L., Hartnett, E., ... Rose, J. B. (2024). Research gaps and priorities for quantitative microbial risk assessment (QMRA). *Risk Analysis, 1*–16. <https://doi.org/10.1111/risa.14318>